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Clinical Pharmacokinetics and Pharmacodynamics of Propofol

Marko M. Sahinovic^{1,3} · Michel M. R. F. Struys^{1,2} · Anthony R. Absalom¹

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Abstract Propofol is an intravenous hypnotic drug that is used for induction and maintenance of sedation and general anaesthesia. It exerts its effects through potentiation of the inhibitory neurotransmitter γ -aminobutyric acid (GABA) at the GABA_A receptor, and has gained widespread use due to its favourable drug effect profile. The main adverse effects are disturbances in cardiopulmonary physiology. Due to its narrow therapeutic margin, propofol should only be administered by practitioners trained and experienced in providing general anaesthesia. Many pharmacokinetic (PK) and pharmacodynamic (PD) models for propofol exist. Some are used to inform drug dosing guidelines, and some are also implemented in so-called target-controlled infusion devices, to calculate the infusion rates required for user-defined target plasma or effect-site concentrations. Most of the models were designed for use in a specific and well-defined patient category. However, models applicable in a more general population have recently been developed and published. The most recent example is the general purpose propofol model developed by Eleveld and colleagues. Retrospective predictive performance evaluations

show that this model performs as well as, or even better than, PK models developed for specific populations, such as adults, children or the obese; however, prospective evaluation of the model is still required. Propofol undergoes extensive PK and PD interactions with both other hypnotic drugs and opioids. PD interactions are the most clinically significant, and, with other hypnotics, tend to be additive, whereas interactions with opioids tend to be highly synergistic. Response surface modelling provides a tool to gain understanding and explore these complex interactions. Visual displays illustrating the effect of these interactions in real time can aid clinicians in optimal drug dosing while minimizing adverse effects. In this review, we provide an overview of the PK and PD of propofol in order to refresh readers' knowledge of its clinical applications, while discussing the main avenues of research where significant recent advances have been made.

Key Points

Propofol is a potent intravenous hypnotic drug. It exerts its effects through potentiation of the inhibitory neurotransmitter, γ -Aminobutyric acid (GABA). Much experience with its clinical use has been amassed since it was introduced over three decades ago.

A general purpose pharmacokinetic (PK) and pharmacodynamic (PD) propofol model recently published by Eleveld and colleagues might replace PK/PD models currently used in clinical practice.

Defining the nature of interaction between propofol and other drugs remains a challenge. Response surface model studies can help to elucidate these interactions.

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1 Introduction

Propofol (2,6-diisopropylphenol) is a potent intravenous hypnotic drug that was developed by Imperial Chemical Industries Limited (London, UK), patented by John (Iain) Glen and Roger James in 1977 [1], and commercially launched in 1986 in Europe and 1989 in the US [2].

Like most anaesthetics, propofol is a γ -aminobutyric acid (GABA) receptor agonist. It has a favourable pharmacokinetic (PK) and pharmacodynamic (PD) profile, which has resulted in it becoming the most commonly used intravenous anaesthetic for the past three decades [2–7]. Rapid and smooth induction with nearly no excitation phenomena, relatively short context-sensitive time, rapid terminal half-life time and low incidence of postoperative nausea and vomiting (PONV) make it a very versatile hypnotic drug. It is used for sedation and anaesthesia for almost all types of surgery, but is particularly well-suited for anaesthesia in patients undergoing ambulatory [8] and neurosurgery where rapid psychomotor recovery are of upmost importance. Its efficacy and utility has also been proven for sedation of patients in the intensive care unit (ICU) [9] and conscious sedation of patients undergoing diagnostic or invasive procedures [10].

The adverse effects of propofol are well-documented, with the most common being pain on injection. Other adverse effects are cardiovascular (bradycardia, hypotension) and metabolic (hyperlipidaemia secondary to infusion of lipid formulation) [11].

Although propofol is well-established in clinical practice, there have been a number of studies published in recent years on the clinical use and pharmacology of the drug. The main aim of this narrative review is to refresh readers' knowledge of the drug, its clinical uses, PK and PD, and to update the reader on the advances in two main fields of research, namely compartmental PK/PD modelling and drug interaction modelling of propofol.

2 Methods

A MEDLINE database search was performed using PubMed. The following 'propofol' Medical Subject Heading (MeSH) terms were used: 'administration and dosage' OR 'adverse effects' OR 'blood' OR 'cerebrospinal fluid' OR 'chemical synthesis' OR 'chemistry' OR 'contraindications' OR 'metabolism' OR 'pharmacokinetics' OR 'pharmacology' OR 'physiology' OR 'poisoning' OR 'therapeutic use' OR 'toxicity' OR 'urine'. All articles published after 1 January 1985, in English, with full-text available and relating to human subjects were evaluated for relevancy. A full-text copy was obtained for

all relevant publications. A further search of the bibliographies of all relevant articles was performed (also known as the snowball method) to identify any relevant publications missed during the initial search. Finally the 'Google Scholar' web search engine was used, with comparable search terms, to complete the literature search.

3 Drug Formulation

Propofol is insoluble in water [4]. It was first marketed in a formulation containing the surfactant Cremophor EL (polyethoxylated castor oil); however, the vehicle was soon changed to a lipid emulsion because of a high incidence of anaphylactic reactions, thought to be caused by Cremophor® [4]. The Diprivan® (AstraZeneca, London, UK) formulation of propofol came on to the market in 1989 in the US and is still available today worldwide. It is formulated as an Intralipid®-based emulsion (Fresenius Kabi, Bad Homburg, Germany) and thus contains the same ingredients, namely soybean oil (100 mg/mL), glycerol (22.5 mg/mL), and egg lecithin (12 mg/mL), and of course propofol as the active ingredient [12]. After a series of reports of bacterial contamination of opened ampoules, ethylenediaminetetraacetic acid (EDTA; 0.05 mg/mL) was added to the formulation in 1996 [13], and is still sold in some but not all countries. The solution is isotonic, and neutral pH is achieved by adding sodium hydroxide. The pK_a is 11.1 at 20 °C [14]. It has a melting point of 18 °C and should therefore be stored at room temperature. A number of different formulations of propofol are currently available, produced by many different manufacturers.

Most propofol formulations cause pain on injection, which is thought to be due to direct and indirect irritation of venous adventitia by free aqueous propofol through an interaction with TRPV1 and TRPA1 receptors [15, 16]. The free aqueous concentration of propofol is thought to be reduced when it is prepared in a solution containing more medium chain triglycerides than in Intralipid®. Therefore, some manufacturers produced and sold generic propofol formulations, such as Propoven® (Fresenius-Kabi, Bad Homburg, Germany) and Propofol-Lipuro® (B-Braun, Melsungen, Germany), containing more medium and fewer long chain-length fatty acids [17]. Although this reformulation of propofol has reduced the prevalence of pain on injection during the induction of anaesthesia, it still remains a problem in clinical practice [18].

4 Indications, Contraindications, Drug Dosing Regimen and Adverse Effects

Propofol is used for the induction and maintenance of the hypnotic component of sedation or general anaesthesia. Its use is contraindicated in two patient categories: (1) patients with hypersensitivity to propofol or any of the components of its formulation, and (2) patients with fat metabolism disorders. Since a small number of case reports of anaphylactic and anaphylactoid reactions have been published, the Diprivan[®] package insert also advises against Diprivan[®] use in patients with allergies to eggs, egg products, soy beans or soy products [19]. However, in two large retrospective studies, Asserhøj and colleagues were unable to confirm the link between propofol and food allergies [20].

Propofol should only be administered by healthcare professionals trained in the safe care of patients undergoing general anaesthesia. During any procedure involving sedation or anaesthesia with propofol, the anaesthetist should closely monitor, and act on any changes in, the patient's physiological parameters according to the American Society of Anesthesiologists (ASA) guidelines on minimum monitoring standards [21]. Multiple propofol dosing schemes exist; however, due to considerable variability in the propofol dose necessary to achieve certain clinical endpoints, these should only be regarded as very approximate dosing guidelines. Propofol administration should always be titrated according to clinical effect, which is part of the reason why the clinician should closely monitor the effects and adverse effects of propofol (*vide infra*). In healthy adults younger than 55 years of age, the Diprivan[®] package insert advises an induction dose of 2–2.5 mg/kg, administered in boluses of 40 mg every 10 s, titrated to the onset of hypnotic effect, and a maintenance dose of 6–12 mg/kg/h. This dose should be adjusted (reduced) when propofol is administered to less-fit patients undergoing general anaesthesia, such as those fulfilling the ASA physical status categories ASA 3 or 4, or when propofol is used to induce and maintain sedation in critically ill patients in the ICU. For exact dosing guidelines, please refer to the package insert.

The main adverse effects of propofol administration relate to alterations of cardiopulmonary physiology, including loss of airway reflexes, hypoventilation or even apnoea, and hypotension. Any provider of anaesthesia should be trained in managing these adverse effects. A rare but serious adverse effect of propofol administration is the 'propofol infusion syndrome' (PRIS), which comprises severe metabolic acidosis, rhabdomyolysis, hyperkalaemia and cardiovascular collapse, and is frequently fatal. PRIS occurs mostly in the setting of prolonged and high-dose

propofol infusion administration in children. The Diprivan[®] package insert advises against administration of propofol > 5 mg/kg/h for more than 48 h. Lastly, there are strong indications, mainly from animal studies [22] and retrospective clinical studies [23], that sedation with GABA agonistic drugs might be responsible for neurotoxicity in paediatric patients, resulting in long-term cognitive deficits; however, clinical significance of these findings is not known and further prospective studies are currently being conducted.

5 Pharmacokinetics (PK)

5.1 Absorption

Propofol is only suitable for intravenous use. It is not suitable for enteral or other routes of administration due to its bitter taste and low oral bioavailability caused by a high first-pass effect and the high hepatic extraction rate (> 90%) [24]. Some researchers have tried to increase the oral bioavailability of propofol, with some success, by administering it in nanoparticles, but this application remains experimental [25].

5.2 Distribution

After intravenous administration, propofol is extensively bound to the plasma proteins (predominantly albumin) and erythrocytes. The free fraction is only 1.2–1.7%. As up to 50% of propofol is bound to the erythrocytes [26], many clinical PK investigators measure whole concentrations rather than plasma propofol concentrations.

Propofol readily crosses the blood–brain barrier (BBB) and causes rapid loss of consciousness (sometimes within the time it takes for a drug to pass through the circulation once [27]). The speed of induction depends on patient-related factors (cardiac output being one of the most important factors) and speed of infusion.

Whereas approximately 1% of total plasma propofol is unbound, free fraction of propofol in the CSF is approximately 31% [28]. Equilibrium between blood and brain concentrations is reached after 30 min, resulting in a total blood to CSF propofol ratio of 0.01–0.02 [29]. Placenta transfer is also fast and extensive, with venous blood concentration mother-to-foetus ratios ranging from 0.7 to 0.8 [30]; however, due to its clearance from the neonatal circulation, it has only minimal and short-lived clinical effects in unborn neonates [31] and is thus safe for use during caesarean section [32].

After a single bolus, or short infusion, the time to offset of clinical effects is short because of the fast initial distribution. Redistribution to and from a slow compartment

also occurs and is due to the high lipid solubility of propofol. This compartment has a large capacity to absorb propofol, which results in a very large apparent volume of distribution at steady state ($V_{d_{ss}}$; three to four multiples of total body volume), even in non-obese individuals [33]. Nonetheless, even after prolonged administration, the offset of clinical effects is still reasonably fast compared with other intravenous hypnotics because redistribution of drug from the slow compartment is slow compared with the rates of metabolism and excretion.

The context-sensitive decrement time [34] for propofol is thus generally favourable compared with other hypnotics. For a short infusion (< 3 h), the 80% decrement time is < 50 min, whereas for longer infusions (> 12 h) it increases up to 3.5 h [35].

5.3 Metabolism

The liver is the main site of propofol metabolism. The majority of propofol (70%) is conjugated to propofol glucuronide by uridine 5'-diphosphate (UDP) glucuronosyl-transferase. Approximately 29% of propofol is hydroxylated to 2,6-diisopropyl-1,4-quinol (4-hydroxypropofol). A number of different cytochrome P450 (CYP) P450 isoforms are involved in this step. CYP2B6 and, to a lesser extent, CYP2C9 are the major catalysts. Environmental and genetic influences on the CYP2B6 can, at least partially, explain the interindividual variability in hydroxylation of propofol in liver microsomes [36]. Propofol metabolites are subsequently conjugated to form 4-(2,6-diisopropyl-1,4-quinol)-sulphate, 1-(2,6-diisopropyl-1,4-quinol)-glucuronide and 4-(2,6-diisopropyl-1,4-quinol)-glucuronide [37, 38] (for a graphic representation of the metabolic pathway of propofol see Fig. 1). The major metabolites have no hypnotic activity.

Liver is very efficient at propofol metabolism, with a blood extraction ratio of 90%. Because of this efficiency, propofol metabolism depends critically on maintained hepatic perfusion, and any decreases in hepatic blood flow concomitantly decrease the propofol metabolic rate. The mean clearance of propofol is around 2.2 L/min [33], which is higher than the total liver blood flow. Extrahepatic sites of metabolism account for 40% of total propofol clearance, which has been confirmed during studies of propofol metabolism during the anhepatic stage of liver transplantation [39]. The kidneys contribute significantly to propofol metabolism. They have an extraction ratio of 60–70% [40, 41] and account for up to one-third of total propofol metabolism. The small intestines are also metabolically active, with an extraction ratio of 24% [39]. The role of the lungs is still being debated; some studies suggest an active role of the lungs [42], while others do not [40], or state that the lungs are merely a temporary

propofol reservoir and later release propofol from binding sites back into circulation [43].

5.4 Elimination and Excretion

After metabolism, 88% of propofol is excreted within 5 days in the urine. Less than 0.3% of administered propofol is excreted unchanged [33]. The phenolic metabolites rarely (< 1% of patients) result in green discolouration of the urine [44].

Propofol is also excreted through exhalation. The amount of propofol excreted this way is extremely small (of the order of a few parts per billion), but the expired concentration correlates with plasma concentrations. Online estimations of propofol plasma concentration, using measurement of expired concentrations, is thus challenging but feasible [45–47]. B. Braun (Melsungen, Germany) has recently launched a commercially available and clinically certified spectrometer, capable of measuring propofol concentration in exhaled air [48].

5.5 Population PK Modelling

5.5.1 Noncompartmental Modelling

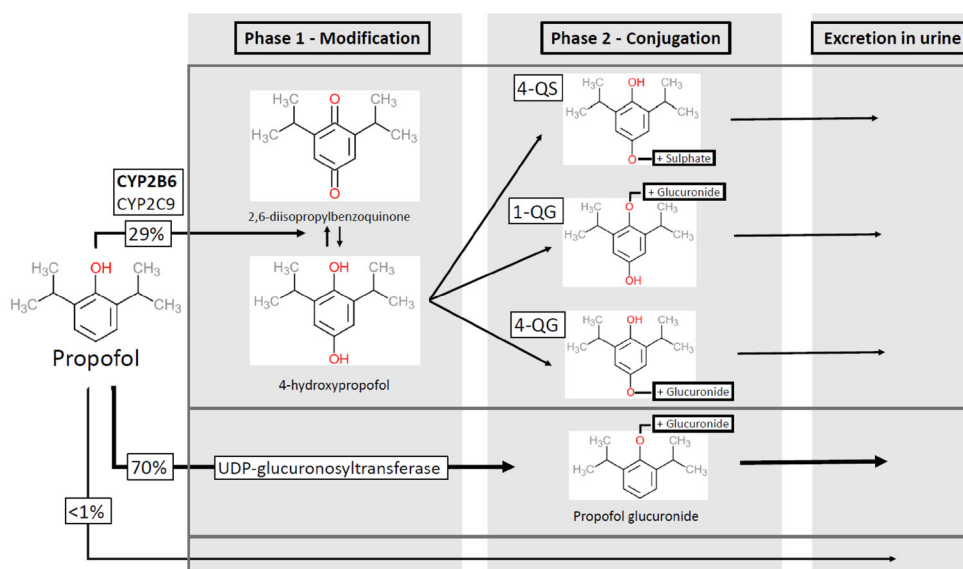
Most of the older studies of the PK of propofol determined only the noncompartmental PK parameters to characterize the PK of propofol. The ranges of published noncompartmental PK parameters for adults after propofol infusion are $V_{d_{ss}}$ 159–771 L, half-life of fast distribution ($T_{1/2\alpha}$) 1.33–4.6 min, half-life of slow distribution ($T_{1/2\beta}$) 27–69.3 min, half-life of elimination ($T_{1/2\gamma}$) 116–834 min, mean residence time (MRT) 102–174 min, total blood clearance (Cl_b) 1.78–2.28 L/min [49–53]

5.5.2 Compartmental Modelling

A PK model is a mathematical means of describing the PK behaviour (distribution and clearance) of a particular drug in the body. PK models are generally used in two ways. First, they can be used to enable the estimation of the drug concentration in the plasma resulting from a given drug administration profile, thereby being useful in advising drug administration rates. Second, they can be used to calculate the necessary infusion rates required to most efficiently achieve and maintain a given drug concentration in a body compartment (in anaesthesia, the plasma or the effect site are targeted) [54].

The most simple compartmental model contains one compartment and two model parameters, namely the volume of distribution (V_d) and clearance. For many drugs, a one-compartment model can adequately describe the PK and guide drug dosing, but for most drugs used in

Fig. 1 Propofol metabolic pathway. *CYP* cytochrome P450, *UDP* uridine 5'-diphosphate



4-QS: 4-(2,6-diisopropyl-1,4-quinol)-sulphate a.k.a. 4-hydroxypropofol-sulphate

1-QG: 1-(2,6-diisopropyl-1,4-quinol)-glucuronide a.k.a. 1-hydroxypropofol-glucuronide

4-QG: 4-(2,6-diisopropyl-1,4-quinol)-glucuronide a.k.a. 4-hydroxypropofol-glucuronide

anaesthesia this is not the case. Therefore, most PK propofol models consist of two or three compartments and a matching number of intercompartmental constants (see Fig. 2 for a diagram of a three-compartment PK and PD model) [55].

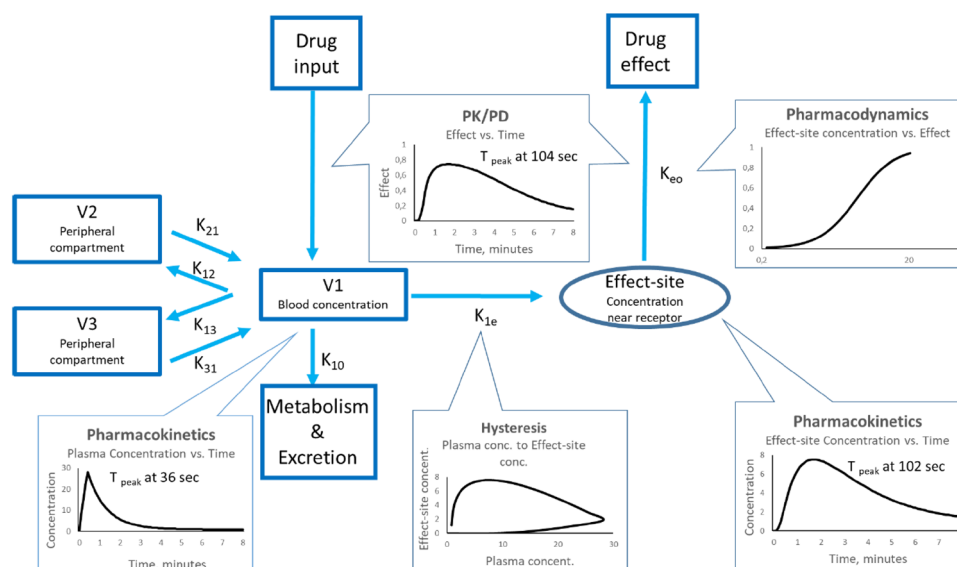
Whether PK models are used to predict achieved concentrations or calculate required infusion rates, a current challenge is to develop models that adequately describe the PK of a widely varying patient population. Obesity is a growing problem, therefore an important issue that needs to be addressed is how to adequately describe patient size so that the PK model compartments and parameters can be effectively scaled to patients with varying sizes and body compositions. A number of different size descriptors exist; body mass index (BMI), ideal body weight (IBW) and adjusted body weight (ABW) are just a few examples. For highly lipophilic drugs, the best size descriptor of volume is probably total body weight (TBW), or another descriptor that incorporates fat mass, while the best size descriptor for clearance is fat free mass [56].

Another challenge is to determine the best way to scale the model compartments and volumes to size (and other) descriptors. Historically, model components were scaled linearly to the size descriptor. This method works well for the intermediate range of sizes but produces erroneous predictions at the extremes of weights, e.g. in small children or morbidly obese adults. Recently, the use of allometric scaling of model components to the size descriptor has become more popular [57]. Allometry is the study of the relationship of size to different anatomical and

physiological aspects of an organism. This relationship was first suggested by Snell [58], while the terminology was coined by Huxley and colleagues [59]. Allometric models scale model components to size using a power exponent with an equation in the form of ' $y = bx^a$ ' where ' y ' is a value of the model component, ' b ' is a constant, ' x ' is the value of the size descriptor and ' a ' is the power exponent (which is commonly 0.75) [60]. Allometric scaling enables generation of universal PK models that are applicable in wide range of patient populations [61, 62]. In general, allometric scaling, often with a power exponent of 0.75, has been shown to apply to multiple biological processes for a wide range of species, from small organisms all the way through to large mammals [63]. However, among neonatal humans, in addition to scaling to size, maturation of enzymatic processes is also an important factor limiting metabolic clearance. Different approaches have been used to deal with this. One approach applied by some groups [60] has been to use different exponents for very young humans. Our group has instead used the same exponent to scale for size, but in addition also applies a sigmoidal function that increases over the course of maturation to the calculation of metabolic clearance in order to correct for the immaturity of metabolic functions in neonates [61, 62].

Although the different models have a similar structure, there are differences in the number of covariates, and in scaling of the volumes and/or clearances in relation to these covariates (see Tables 1 and 2 for study methods and model equations derived from different models). Many models were developed for widely differing patient

Fig. 2 Overview of a three-compartment pharmacokinetic/pharmacodynamic model



Intercompartmental transfer constants:

$$K_{21}/K_{12} = CL_2$$

$$K_{31}/K_{13} = CL_3$$

categories, but, to our knowledge, propofol PK have not been studied in critically ill ICU patients; thus, none of the existing PK models applies to these patients.

5.5.2.1 Adult Population Many adult PK models for propofol have been published. Large variability among the model parameters can be found due to differences in study design, drug administration profile and study population used to develop the model [64]. Although numerous multicompartamental mammillary models exist, only two adult models are commonly used in clinical practice for target-controlled infusions (TCIs), namely the Marsh [65] and Schnider [66] models.

In the Marsh model, the volumes (V_1 , V_2 , V_3) are a linear function of patient weight, while the intercompartmental transfer rates (k_{12} , k_{21} , k_{13} , k_{31}) are constant. In contrast, the Schnider model has fixed V_1 , V_3 , k_{13} and k_{31} , and uses age as a covariate in the calculation of V_2 , k_{12} and k_{21} , and lean body weight, sex, total body mass and height as covariates of the metabolic clearance.

As indicated above, a benefit of the Schnider model over the Marsh model is that it adjusts the dose and infusion rate according to the patient's age. This results in smaller bolus doses administered by the TCI pump (on starting, or when the target concentration is increased) in older patients, which might improve haemodynamic stability. A disadvantage of the Schnider model is that the lean body mass equation incorporated into the calculation of k_{10} can generate paradoxical values, resulting in excessive increases in maintenance infusion rates in the obese [67].

In general, both models have acceptable performance in daily practice, and the choice of model to use is predominantly made based on user experience and the model availability.

5.5.2.2 Obese Population Obesity is associated with a number of physiological and pathophysiological changes that can have a significant impact on drug PK. The most important factors affecting PK in obese patients are changes in body composition, haemodynamics, regional blood flow, and liver and kidney function [68].

Older propofol models, such as the Marsh [65] and Schnider [66] models, were developed from studies involving healthy adults with a limited range of weights. Some practitioners still use the Marsh model [65] for TCI propofol administration in obese patients [67], but instead of inputting the TBW, they input an ABW calculated from the TBW and IBW, and calculated as follows:

$$ABW = IBW + 0.4 \times (TBW - IBW).$$

where IBW is calculated as:

$$IBW = 45.4 + 0.89 \times (HT [cm] - 152.4) + 4.5(\text{if male})$$

or more simply as:

$$IBW = \text{height [cm]} - 100 (\text{if male}) \text{ or } IBW = \text{height [cm]} - 105 (\text{if female}).$$

As mentioned earlier, in severely obese patients, the LBM equation used in the Schnider model generates paradoxically large increases in the k_{10} , when the BMI

Table 1 Methods

| Principal investigator (publication year) | Population characteristics | | | | Setting | Comedication | Target population | | |
|--|----------------------------|-----------------------------|-------------------------------------|-----------------------------|---------------------------|---|-------------------|-------|------------|
| | Sex (M/F) | Age (years) ^a | TBW (kg) ^a | Height (cm) ^a | | | Adults | Obese | Paediatric |
| Gepts [49] (1987) | 13/5 | 29–65 | 49–82 | 155–175 | PTN | Glycopyrrolate 0.4 mg IM, lidocaine/bupivacaine intrathecal | X | | |
| Marsh [65] (1991) | Idem Gepts | Idem Gepts | Idem Gepts | Idem Gepts | Idem Gepts | Idem Gepts | X | | |
| Kataria [74] (1994) | 28/25 | 3–11 | 15–61 | NA | PTN | Rocuronium, fentanyl, atropine, bupivacaine, neostigmine + atropine | | | X |
| Short [75] (1994) | 6/4 | 4–7 | 15–22 | NA | PTN | EMLA, N ₂ O, bupivacaine wound infiltration | | | X |
| Schnider [66] (1998) | 13/11 | 26–81 | 44–123 | 155–196 | HV | No comedication administered | X | | |
| Schuttler [52] (2000) | 150/ 120 | 2–88 | 12–100 | – | PTN and HV | X1 | X | | X |
| Knibbe [78] (2005) | R: 24 C: 6 A: 24 | R: x C: 1–5 A: 37–73 | R: 0.25–0.3 C: 10–21 A: 64–93 | – | R: HV C: PTN A: PTN | X2 | X | | |
| Paedfusor [73] (2005) | NA | NA | NA | NA | NA | Yes, details not published | | | X |
| van Kralingen [70] (2006) | 20/44 | 48.5 | 55–167 | – | PTN | Lidocaine, fentanyl, atracurium, remifentanyl | X | X | |
| Cortínez [69] (2010) | 7/11 | 28–56 | 82–134 | 139–185 | PTN | X3 | X | X | |
| Elefeld [72] (2018) | 672/ 361 | 0–88 | 0.68–160 | NA | PTN and HV | X4 | X | X | X |
| Sahinovic [149] (2017) | 21/19 | 53 | 81.5 | 175.5 | PTN | Rocuronium | X | | |

X1: multiple datasets were analysed (Schuttler [52], Cockshott [51, 190], Glass [184], White [65, 191], Shafer [74]). Each dataset involved patients receiving different comedications

X2: Multiple datasets were analysed (Cox [192], Knibbe [193], Knibbe [194], Knibbe [195]). Each dataset involved patients receiving different comedications

X3: Multiple datasets were analysed (Schnider [66], Servin [196], Cortínez [69]). Each dataset involved patients receiving different comedications

X4: Data from 30 previously published studies were used. Each dataset involved patients receiving different comedications

HV healthy volunteers, PTN patient, R rat, C children, A adults, NA not available, TBW total body weight, M male, F female, IM intramuscularly

^aRange/average

is > 37 in females and > 42 in males [67]. As a result, commercially available TCI devices programmed with the Schnider model do not allow the user to input parameters that generate BMI values above these limits. Users attempting to use the Schnider model in severely obese patients must either change to a different model, enter a 'false' combination of parameters (i.e. a greater height or a lower weight in place of the TBW), or administer propofol by manually controlled infusion.

There are currently a number of propofol models specifically developed for obese patients, such as the Cortínez [69] and van Kralingen [70] models, or a general

purpose model that is probably also suitable for use in the obese (the Elefeld allometric model) [61] (see Table 1).

Cortínez et al. [71] have investigated the predictive performance of different PK models in obese patients and concluded that when models were implemented as published (i.e. using the TBW as a weight-scaling measure), the global performance of the Elefeld model [72] was best compared with other models. All models tended to underestimate the propofol plasma concentration. When the user entered the ABW instead of the TBW, the Schnider and Marsh models had the highest accuracy and lowest bias [71].

Table 2 Model equations

| Gepts [49] | | Marsh [65] | |
|----------------------------------|---|----------------------------------|---|
| V_1 | 16.92 L | V_1 | $0.228 \times \text{TBW}$ |
| V_2 | 35.07 L | V_2 | $0.464 \times \text{TBW}$ |
| V_3 | 215.3 L | V_3 | $2.89 \times \text{TBW}$ |
| $K_{10} (\text{min}^{-1})$ | 0.119 | $K_{10} (\text{min}^{-1})$ | 0.119 |
| $K_{12} (\text{min}^{-1})$ | 0.114 | $K_{12} (\text{min}^{-1})$ | 0.112 |
| $K_{13} (\text{min}^{-1})$ | 0.0419 | $K_{13} (\text{min}^{-1})$ | 0.042 |
| $K_{21} (\text{min}^{-1})$ | 0.0550 | $K_{21} (\text{min}^{-1})$ | 0.055 |
| $K_{31} (\text{min}^{-1})$ | 0.0033 | $K_{31} (\text{min}^{-1})$ | 0.0033 |
| Kataria [74] | | Short [75] | |
| V_1 | $0.41 \times \text{TBW}$ | V_1 | $0.432 \times \text{TBW}$ |
| V_2 | $0.78 \times \text{TBW} + 3.1 \times \text{AGE} - 16$ | V_2 | |
| V_3 | $6.9 \times \text{TBW}$ | V_3 | |
| $\text{CL1 (L min}^{-1}\text{)}$ | $0.035 \times \text{TBW}$ | $K_{10} (\text{min}^{-1})$ | 0.0967 |
| $\text{CL2 (L min}^{-1}\text{)}$ | $0.077 \times \text{TBW}$ | $K_{12} (\text{min}^{-1})$ | 0.1413 |
| $\text{CL3 (L min}^{-1}\text{)}$ | $0.026 \times \text{TBW}$ | $K_{13} (\text{min}^{-1})$ | 0.0392 |
| | | $K_{21} (\text{min}^{-1})$ | 0.1092 |
| | | $K_{31} (\text{min}^{-1})$ | 0.0049 |
| Schnider [66] | | Schuttler [52] | |
| V_1 | 4.27 L | V_1 | $9.3 \times (\text{TBW}/70)^{0.71} \times (\text{Age}/30)^{-0.39}$ $\times (1 + \text{BOL} \times 1.61)$ |
| V_2 | $18.9 + (-0.391 \times (\text{Age} - 53)) \text{ L}$ | V_2 | $44.2 \text{ L} \times (\text{TBW}/70)^{0.61} \times (1 + \text{BOL} \times 0.73)$ |
| V_3 | 238 L | V_3 | 266 L |
| $\text{CL1 (L min}^{-1}\text{)}$ | $(1.89 + ((\text{TBM}-77) \times 0.0456$ $+ ((\text{LBM}-59) \times -0.0681)$ $+ ((\text{HT}-177) \times 0.0264))$ | $\text{CL1 (L min}^{-1}\text{)}$ | $\text{Age} \leq 60: 1.44 \text{ L/min} \times (\text{TBW}/70)^{0.75}$ $\text{Age} > 60: 1.44 \times (\text{TBW}/70)^{0.75}$ $- (\text{Age} - 60) \times 0.045$ |
| $\text{CL2 (L min}^{-1}\text{)}$ | $1.29 + (-0.024) \times (\text{Age} - 53)$ | $\text{CL2 (L min}^{-1}\text{)}$ | $2.25 \text{ L/min} \times (\text{TBW}/70)^{0.62} \times (1 + \text{VEN}$ $\times -0.40) \times (1 + \text{BOL} \times 2.02)$ |
| $\text{CL3 (L min}^{-1}\text{)}$ | 0.836 | $\text{CL3 (L min}^{-1}\text{)}$ | $0.92 \text{ L/min} \times (\text{TBW}/70)^{0.55} \times (1 + \text{BOL}$ $\times -0.48)$ |
| Reference | Males: $\text{LBM} = 1.1 \times \text{WT} - 128 \times (\text{WT}/\text{HT})^2$; Females: $\text{LBM} = 1.07 \times \text{WT} - 148 \times (\text{WT}/\text{HT})^2$ | Reference | $\text{VEN} = 1$ for venous sample and 0 for arterial sample; $\text{BOL} = 1$ for bolus data and 0 for infusion data |
| Knibbe [78] | | Paedfusor [73] | |
| V_1 | $0.3 \times \text{TBW}^{0.98}$ | V_1 | $0.4584 \times \text{TBW}$ |
| V_2 | $1.2 \times \text{TBW}^{1.1}$ | V_2 | $V_1 \times k_{12}/k_{21}$ |
| $\text{CL1 (L min}^{-1}\text{)}$ | $0.071 \times \text{WT}^{0.78}$ | V_3 | $V_1 \times k_{13}/k_{31}$ |
| $\text{CL2 (L min}^{-1}\text{)}$ | $0.062 \times \text{WT}^{0.73}$ | $K_{10} (\text{min}^{-1})$ | $0.1527 \times \text{TBW}^{-0.3}$ |
| | | $K_{12} (\text{min}^{-1})$ | 0.114 |
| | | $K_{13} (\text{min}^{-1})$ | 0.0419 |
| | | $K_{21} (\text{min}^{-1})$ | 0.055 |
| | | $K_{31} (\text{min}^{-1})$ | 0.0033 |

Table 2 continued

| Kralingen et al. [70] | | Cortínez [69] | |
|-----------------------------------|---|-----------------------------------|--|
| V_1 | 3.03 L | V_1 | $4.48 \times (\text{TBW}/70) \text{ L}$ |
| V_2 | 5.34 L | V_2 | $21.2 \times (\text{TBW}/70) \times e^{-0.0164 \times (\text{Age}-50)} \text{ L}$ |
| V_3 | 116 L | V_3 | $237 \times (\text{TBW}/70) \text{ L}$ |
| $\text{CL}_1 (\text{L min}^{-1})$ | $2.22 \times (\text{TBW}/70)^{0.67}$ | $\text{CL}_1 (\text{L min}^{-1})$ | $1.92 \times (\text{TBW}/70)^{3/4}$ |
| $\text{CL}_2 (\text{L min}^{-1})$ | 1.64 | $\text{CL}_2 (\text{L min}^{-1})$ | $1.45 \times (\text{TBW}/70)^{3/4} \times e^{-0.0153 \times (\text{Age}-50)}$ |
| $\text{CL}_3 (\text{L min}^{-1})$ | 1.86 | $\text{CL}_3 (\text{L min}^{-1})$ | $0.86 \times (\text{TBW}/70)^{3/4}$ |
| Eleveld [72] | | Sahinovic [149] | |
| $V_{1 \text{ arterial}}$ | $6.25 \times f_{\text{central}}(\text{WGT})/f_{\text{central}}(\text{WGT}_{\text{ref}}) \times e^{0.61}$ | V_1 | $3.8 \times (\text{TBW}/70) \times e^{0.205}$ |
| $V_{1 \text{ venous}}$ | $V_{1 \text{ arterial}} \times (1 + 1.42 \times (1 - f_{\text{central}}(\text{WGT})))$ | V_2 | $9.21 \times (\text{TBW}/70) \times e^{0.268}$ |
| V_2 | $25.5 \times \text{WGT}/\text{WGT}_{\text{ref}} \times f_{\text{aging}}(-0.0156) \times e^{0.565}$ | V_3 | $447 \times (\text{TBW}/70)$ |
| V_3 | $273 \times f_{\text{FFM}}/f_{\text{FFM,ref}} \times f_{\text{opiates}}(-0.0138) \times e^{0.597}$ | $\text{CL}_1 (\text{L min}^{-1})$ | NT: $1.33 \times (\text{TBW}/70)^{0.75} \times e^{0.00902}$ T: $1.33 \times (\text{TBW}/70)^{0.75} \times 1.444 \times e^{0.00902}$ |
| CL_{male} | $1.79 \times (\text{WGT}/\text{WGT}_{\text{ref}})^{0.75} \times f_{\text{CLmaturity}}/f_{\text{CLmaturity,ref}} \times f_{\text{opiates}}(-0.003) \times e^{0.265}$ | $\text{CL}_2 (\text{L min}^{-1})$ | $0.987 \times (V_2/9.21)^{0.75}$ |
| $\text{CL}_{\text{female}}$ | $2.1 \times (\text{WGT}/\text{WGT}_{\text{ref}})^{0.75} \times f_{\text{CLmaturity}}/f_{\text{CLmaturity,ref}} \times f_{\text{opiates}}(-0.003) \times e^{0.265}$ | $\text{CL}_3 (\text{L min}^{-1})$ | $1.37 \times (V_3/447)^{0.75} \times e^{0.192}$ |
| $\text{Q}_2^{\text{arterial}}$ | $1.75(V_2/V_{2\text{ref}})^{0.75} \times (1 + 1.3 \times (1 - f_{\text{Q3maturity}})) \times e^{0.346}$ | | |
| $\text{Q}_2^{\text{venous}}$ | $\text{Q}_2^{\text{arterial}} \times 0.68$ | | |
| Q_3 | $1.11 \times (V_3/V_{3\text{ref}})^{0.75} \times f_{\text{Q3maturity}}/f_{\text{maturity,ref}} \times e^{0.209}$ | | |
| Reference | $f_{\text{aging}}(x) = e^{(x \times (\text{AGE}-\text{AGE}_{\text{ref}}))}$ $f_{\text{sigmoid}}(x, \text{E50}, \lambda) = x^\lambda/(x^\lambda + \text{E50}^\lambda)$ $f_{\text{central}}(x) = f_{\text{sigmoid}}(x, 33.6, 1)$ $f_{\text{CLmaturity}} = f_{\text{sigmoid}}(\text{PMA}, 42.3, 9.06)$ $f_{\text{Q3maturity}} = f_{\text{sigmoid}}(\text{AGE} + 40 \text{ weeks}, 68.3, 1)$ $f_{\text{opiates}}(x) = 1, \text{ absence}$ $f_{\text{opiates}}(x) = e^{(x \times \text{AGE})}, \text{ presence}$ $\text{FFM}_{\text{males}} = [0.88 + (1 - 0.88)/1 + (\text{AGE}/13.4)^{-12.7}] \times [9270 \times \text{WGT}/6680 + 216 \times \text{BMI}]$ $\text{FFM}_{\text{females}} = [1.11 + (1 - 1.11)/1 + (\text{AGE}/7.1)^{-1.1}] \times [9270 \times \text{WGT}/8780 + 244 \times \text{BMI}]$ | Reference | T: Patients with brain tumour NT: patients without brain tumour |

$\text{CL}_1 = V_1 \times K_{10}$; $\text{CL}_2 = V_2 \times K_{21}$; $\text{CL}_3 = V_3 \times K_{31}$; $V_2 = V_1 \times K_{12}/K_{21}$; $V_3 = V_1 \times K_{13}/K_{31}$

M male, F female, Y young, E elderly, TBW total body weight, FFM fat-free mass, PMA postmenstrual age

5.5.2.3 Paediatric Population Develop PK models for children is challenging, for many reasons. First, there are ethical challenges with research in children, and, second, as children grow, their size increases, their body composition changes and their organ systems mature, making it difficult to construct a single and accurate PK model.

A number of paediatric PK models for propofol exist, the most well-known being the Paedfusor model [73], Kataria model [74], Short model [75], Schüttler model [52] and the Eleveld ‘general purpose’ model [72]. These models were developed using a range of methodologies. Differences in methodology include the age range of the children enrolled in the study, the study population (healthy

children as opposed to children with comorbidities), the sampling site (arterial vs. venous) and the administration regimens used (bolus with or without continuous infusion thereafter). These differences influence the range of patients to which the different models are applicable. For example, the Kataria model was developed from children 3 years of age and older and is thus not validated for use in children younger than 3 years of age.

Sepúlveda et al. [76] and Hara et al. [77] evaluated the predictive performance of these models during short- and long-duration infusions, respectively, and concluded that overall most models overestimate the initial Vd. The relevance is that when they are used to inform dosing schemes

designed to achieve a particular plasma concentration, they result in administration of a larger than necessary induction bolus. Most paediatric models performed well during infusions of short duration (up to median of 99 min), while only the Short [75] and Schüttler [52] models showed acceptable performance and the least divergence during infusions of up to 545 min. Overall, the Short model performed the best and the authors concluded that it might be preferable for use during TCI in children.

5.5.2.4 Unified PK Models A PK model is only applicable in patients in whom the clinical conditions and patient category match those used in model development. As soon as these begin to diverge, model predictions can be erroneous. Using an inappropriate model during a TCI can lead to unexpected (side) effects. Rational model selection is of critical importance, but given the large number of available models, this is not an easy task. Furthermore, an exact match is often not possible. Even for users knowledgeable in PK, it is difficult to be certain which models to use in patients with overlapping conditions (e.g. patients who are elderly and obese), or in grey zones between conditions (e.g. patients who are moderately obese but otherwise healthy). These difficulties have stimulated the development of unified PK models, which are derived from data collected in a diverse group of patients and clinical conditions, and are thus designed to provide accurate predictive performance well in a wide range of patients and clinical conditions.

The first unified PK model for propofol was published by Schüttler and Ihmsen [52] in 2000. This group developed a general PK model for propofol, applicable in both children and adults, by performing PK analysis on data collected by five different research groups. This analysis yielded a three-compartment PK model with weight, age, method of administration and sampling site as the main covariates. They concomitantly demonstrated that scaling of model compartments and clearances to power exponents (between 0.55 and 0.75) of normalized TBW yielded better model predictions than that of linear scaling. An important obstacle to a broader clinical application of this model is the fact that the user must select a mode of administration (bolus vs. continuous infusion) before using the model, whereas in clinical practice both administration modes are often used.

In 2005, Knibbe and colleagues [78] published an interspecies PK model for propofol, which was a two-compartment model applicable in rats, children and adults. They achieved this impressive task by allometrically scaling volumes and clearances to TBW. In other words, they scaled the volumes and clearances in the model to a power exponent (between 0.73 and 1.1), which allowed them to more realistically estimate the volumes and

clearances in a wide range of different bodyweights, from a small rat weighing 0.25 kg to an adult weighing 93 kg.

The most recently published unified PK model for propofol is the 'general purpose model' constructed by Eleveld and colleagues [61]. First published in 2014, the PK model was recently expanded with a PD analysis [72]. In the updated version of the model, the authors used PK data derived from 30 previously published studies containing data collected from children of all ages, adults, obese adults, and elderly individuals. They constructed a three-compartment model where weight, age, sex and administration of comedication were covariates. Similar to the work of Schüttler and Ihmsen [52] and Knibbe et al. [78], they also used allometric scaling to normalize bodyweight for clearances (three-quarter power exponent), while volumes were scaled linearly with normalized body weight for V_1 and V_2 , and with normalized fat-free mass for V_3 . Retrospective analysis of this model performance shows that the model performs at least as good as, or better, than dedicated population models in all populations. Further model evaluation must be performed in prospective studies.

5.5.3 Effects of Patient Characteristics on Propofol Kinetics

One of the main advantages of analysing a larger set of PK and PD data from a wide range of patients is the ability to detect covariate relationships that might remain hidden when a dataset from patients with a narrower range of characteristics is analysed. As a result, Eleveld et al. were able to identify a few, clinically very relevant, correlations. They found a relationship between age and the volume of the peripheral compartments and metabolic clearance. The volume of V_2 declines with age, while V_3 and metabolic clearance decline only when other medication are concurrently administered. This finding confirms an impression widely shared by practicing anaesthetists that the maintenance infusion rates required for adequate anaesthesia are reduced in older individuals, especially when comedication is administered. Furthermore, they found that the central compartment scales to an E_{\max} function (in other words central compartment volume increase follows a sigmoid function with increasing weight). This suggests that the induction dose of propofol, per kilogram, should be relatively high in low-weight individuals, and relatively low in obese patients, compared with individuals with intermediate weight. This fact is also consistent with the observations of clinical practitioners. Lastly, they reported a higher metabolic clearance in women (of all ages) compared with men, which might explain clinical observations of a more rapid emergence from propofol anaesthesia in women compared with men [79].

5.5.4 Physiologically-Based PK Models

Contrary to compartmental PK models where compartments have no real physiological meaning (or direct correspondence with body parts), compartments in physiologically-based PK models (PBPK) are linked to different body parts connected by the cardiovascular system. Typically, all the major tissues, such as adipose tissue, muscle, brain, heart, kidney, liver, and lung, are represented [80].

An important advantage of PBPK models over compartmental models is the ability of the former to include more parameters specifying sources of physiological and biochemical variability in individuals, thereby reducing the interindividual variability and increasing the individual prediction accuracy. For example, the incorrect assumption of instantaneous mixing of a drug in the central compartment used by compartmental models severely limits their prediction accuracy during the first few minutes of drug infusion. Adaptations to the compartmental models using ‘administration lag time’ and presystemic compartments can improve the prediction accuracy [81], however only PBPK models use cardiac output [82] and blood flow terms to more accurately describe the drug kinetics in greater detail. This even potentially enables them to predict the influence of the effect of changing haemodynamic parameters on drug disposition. The same applies to cerebral blood flow, changes of which can play a major role in propofol PD.

An important disadvantage of PBPK models is the difficulty in collecting the extensive physiological data necessary for model development, and often very limited (if any) improvement in prediction accuracy at a cost of a much more complex and mathematically elaborate model compared with compartmental models [83].

The physiologically-based hybrid recirculatory model published by Upton and Ludbrook [84] is an example of a PBPK propofol model. It incorporates submodels for the lung and brain, and a less detailed ‘lumped model’ for the rest of the body. The prediction accuracy and bias are comparable with that of the major compartmental models [83].

6 Pharmacodynamics (PD)

6.1 Central Nervous System

6.1.1 Hypnotic Effects

Propofol exerts its hypnotic effect through potentiation of the effects of the inhibitory neurotransmitter GABA [85]. It binds to the β -subunit of the postsynaptic GABA_A receptor,

where it causes an inward directed chloride current that hyperpolarizes the postsynaptic membrane and inhibits neuronal depolarization. This effect is dose-dependent. At low concentrations, propofol potentiates GABA-activated inward chloride currents, while at higher concentrations, it directly activates the channel opening [86]. GABA receptors are ubiquitous throughout the central nervous system [87].

Although our understanding of the actions of propofol at the molecular level is quite extensive, we do not entirely understand how these molecular effects translate into alterations in cellular, synaptic and neural network function, and in turn cause unconsciousness [88]. This knowledge gap is, at least in part, the result of a lack of a generally accepted theory of consciousness. In recent years, cognitive neuroscience has seen a resurgence of interest in this topic, with attempts to integrate anaesthesia and sleep research in order to address this deficiency. This resurgence has revealed several brain areas that play a crucial role in generation of consciousness, and which are extensively influenced by hypnotic drugs.

In the reticular formation of the brainstem [89], there are a number of sleep- and wakefulness-promoting cholinergic and monoaminergic nuclei that exert their effect by influencing higher cortical structures [90]. Their activity and reciprocal influence changes with the level of wakefulness [91]. Local inactivation of wakefulness-promoting areas, such as locus coeruleus and dorsal raphe, enhance anaesthesia, while local activation of various other wakefulness-promoting areas, including pontis oralis and centromedial thalamus, facilitate emergence from anaesthesia. One of the sleep-promoting nuclei is the ventrolateral preoptic area. Lesions in this region enhance wakefulness [92]. These nuclei are extensively affected by clinical concentrations of hypnotic drugs.

The thalamus plays a central role in information processing with the brain. Increasing concentrations of propofol, and thereby increasing levels of sedation, cause a decrease in activity, regional cerebral blood flow and metabolism in the thalamus [93]. There are a number of (mutually nonexclusive) hypotheses on how these changes could lead to or contribute to loss of consciousness [94]. The function of the thalamus as a critical sensory information relay from subcortical structures to the cortex could be impeded by hypnotic drugs [95], although thalamic depression seen after loss of consciousness could merely reflect the decrease in global cortical activity [96]. Hyperpolarization of thalamocortical neurons—and the resulting switching from a tonic firing state in wakefulness to a bursting firing state in unconsciousness—could be a final common pathway through which different hypnotics cause a disruption in thalamocortical and cortico-cortical loops, thereby causing unconsciousness [97].

Finally, the cerebral cortex has long been identified as an important drug effect target for hypnotic drugs. Sleep and anaesthesia studies have consistently demonstrated decreases in cortical activity and cerebral blood flow [98]; however, these changes are not homogeneous across the cortex and across different drugs. The most consistent and largest changes occur in the frontal and posterior parietal cortex [99]. These regions form part of a much wider 'default mode network', a functional network thought to be responsible for monitoring of internal environment in humans. Loss of consciousness in non-REM sleep is accompanied by increased modularization of brain activity and reduction in a whole-brain spatiotemporal integration of information [100–102]. This is concordant with the information integration theory of consciousness [103].

6.1.2 Amnesia

The amnesic properties of propofol have been extensively described in the literature [104]. Explicit memory seems to be most affected, and in a dose-dependent manner. The most basic form of memory, perceptual priming, seems to be preserved to some degree [105]. The amnesic effects of propofol do not seem to be caused by interference with memory encoding, but a low-dose of propofol has been shown to induce amnesia without any impairments in behaviour [106]. The exact neural mechanism of propofol-induced amnesia in a conscious patient remains to be elucidated.

6.1.3 Anxiolysis

Propofol produces anxiolysis in subhypnotic doses. This has been demonstrated in mice [107] and in patients undergoing propofol sedation while undergoing surgical procedures under regional anaesthesia [108]. Propofol has been proposed as an excellent preoperative anxiolytic drug in day-care surgery, when administered through a patient-controlled anxiolysis system (a patient-controlled analgesia system analogue), as a replacement for benzodiazepine premedication in order to shorten the discharge times [109]. The exact mechanism of this anxiolysis is still not known, but inhibition of 5-HT activity in the hippocampus [110] or nitric oxide synthase in the hypothalamus, amygdala and hippocampus might be the mechanisms involved [111].

6.1.4 Analgesia

There are a number of patient studies describing the analgesic effects of subhypnotic doses of propofol [112, 113]. This effect could be caused by an action of propofol at the spinal level. In animal studies, it has been shown that

propofol produces analgesia in mice when administered intraperitoneally, through modulation of spinal GABA_A receptors [114], and thereby depresses ventral root potentials in the spinal cord elicited by monosynaptic reflexes or exposure of the spinal cord to substance P [115]. Furthermore, Nishiyama et al. showed that intrathecal injections of propofol had effects on pain perception, but they could not rule out the possibility of neurotoxicity [116].

A recently published meta-analysis comparing postoperative pain after propofol versus inhalation-based anaesthesia did not demonstrate any significant differences, mainly because of substantial heterogeneity among studies published to date [117].

6.1.5 Antiemetic Effect

The antiemetic action of propofol is well known and has been extensively described [118, 119]. Patients receiving anaesthesia with propofol experience significantly less PONV compared with that associated with other hypnotic drugs, irrespective of the use of adjunct drugs, patient characteristics or opiate use. The mechanism behind this effect is not very well understood, but it has been demonstrated that propofol interacts with dopaminergic (D2) receptors in the chemoreceptor trigger zone [120], inhibits the limbic system [121], thereby interacting with cortical reflexes reaching the vomiting centre, and inhibits 5-HT₃ receptors located in the central nervous system in a noncompetitive and dose-dependent manner, thereby reducing the incidence and severity of PONV.

6.1.6 Neurophysiological Effects

Propofol decreases cerebral blood flow, intracranial pressure, and cerebral metabolic rate, while maintaining dynamic and static autoregulation [122] and vascular responsiveness to carbon dioxide [123]. These favourable effects on cerebral physiology make propofol an almost ideal hypnotic for anaesthesia during neurosurgery. The evidence for neuroprotective effects of propofol during ischaemia-reperfusion injury is conflicting [124]; however, its role as part of multimodal neuroprotection has been established [125].

Propofol has both pro- and anticonvulsive activity. On the one hand, a number of reports of convulsions and excitatory events such as myoclonus and tremor, during or shortly after the start or end of propofol anaesthesia, have been published [126]; these events might be the result of preferential depression of subcortical regions. On the other hand, the role of propofol as a potent treatment of status epilepticus has been well-established [127, 128].

6.2 Cardiovascular System

Propofol has extensive effects on the cardiovascular system. The most prominent effect is systemic blood pressure reduction accompanied by a decrease in cardiac output. This effect is dose-dependent and even occurs at sedative doses. It is more pronounced in elderly and physiologically compromised patients [129]. The effect is, at least partially, mediated by a significant decrease of sympathetic tone accompanied by a decrease in vascular resistance. Furthermore, propofol also inhibits the physiological baroreflex responses, thereby enhancing cardiovascular depression [130].

Cardiac contractility remains preserved. Propofol only has direct negative inotropic actions at concentrations exceeding the clinical range, an effect that is similar in failing and non-failing human hearts. The negative inotropic effect is mediated through a concentration-dependent decrease in the uptake of Ca^{2+} into the sarcoplasmic reticulum, which is simultaneously accompanied by an increase of myofilament sensitivity to Ca^{2+} , partially counteracting the effect [131]. The haemodynamic response lags behind the hypnotic effect of propofol. While the hypnotic half-time plasma effect site equilibration time ($T_{1/2}k_{\text{eo}}$) is 2.5 min, independent of age, haemodynamic half-time plasma effect site equilibration time is 5 min in young patients, and up to 10 min in elderly patients [132].

Propofol cardioprotective effects in cardiac surgery is a focus of research. In animal studies, high propofol doses caused dose-dependent attenuation of ischaemia-reperfusion myocardial injury (IRI) by exerting free radical scavenging effects and decreasing lipid peroxidase activity [133]. These cardioprotective effects are less profound than those caused by sevoflurane [134]. A combination of inhaled anaesthetic preconditioning and propofol postconditioning appears to work synergistically in decreasing IRI [135].

6.3 Respiratory System

Propofol is a potent ventilatory depressant. It interferes with ventilation in a dose-dependent manner by affecting central chemoreceptor sensitivity, reducing ventilatory responses to hypercapnia and hypoxia [136–138]. In higher doses, propofol causes apnoea. It also changes the pattern of breathing by decreasing the ribcage contribution to tidal volume [139] by causing upper airway relaxation and suppression of upper airway reflexes [140]. Furthermore, it attenuates vagal- and methacholine-induced bronchoconstriction [141] and potentiates hypoxic pulmonary vasoconstriction [142].

6.4 Hepatorenal System

Despite the fact that the liver and kidneys are extensively involved in metabolism and excretion of propofol, their function does not appear to be affected by propofol. In human and animal studies, propofol infusion increased hepatic perfusion [143] due to higher arterial [144] and portal venous blood flow [145], while renal perfusion remained essentially unaltered [146]. However, when cardiac output is not maintained, organ perfusion, and thus liver and renal perfusion, could be compromised.

Propofol infusion is known to cause green skin and urine discolouration caused by production of phenol green chromophore. Furthermore, urinary uric acid excretion is increased after propofol infusion, which can result in a cloudy appearance of the urine.

6.5 PD Modelling

For propofol, the main clinical effect is loss of consciousness, which is difficult to quantify. Most clinicians consider it to be a continuum of effects, most of which have a binary nature, i.e. present or absent. However, several electroencephalogram (EEG)-based methods of quantifying the depth of anaesthesia have been developed [147, 148]. The most commonly used is the Bispectral index (BIS; Medtronic, Dublin, Ireland), a unitless number between 0 and 100, where 0 represents very high hypnotic drug effect (i.e. no cerebral electrical activity) and 100 represents total absence of the hypnotic drug effect. The BIS monitor is one of the best validated EEG-based monitors for quantifying the drug effect [148]. Several PD studies have been performed, with most of them using a sigmoidal E_{max} model to characterize the relationship between blood concentration, the concentration in a hypothetical effect site, and the resultant clinical drug effect. Published parameters are in the following ranges: k_{eo} , 0.01–0.45 min^{-1} ; Ce_{50} , 2.71–3.44 mg L^{-1} ; and γ , 1.47–2.961 [65, 67, 71, 149–152].

7 Drug Interactions

Interactions between drugs occur in the PK, PD, or both [153]. Alterations in the PD (clinically visible) drug dose–effect relationship can be secondary to PK and/or PD interactions; therefore, these interactions are most often not discussed separately when considering clinical applications. Drug interactions can be additive, synergistic or antagonistic [154]. Any anaesthesia provider should be aware of this and adjust the drug dose accordingly.

7.1 PK Interactions

PK interactions can result in changes in absorption, distribution, metabolism and elimination.

7.1.1 Absorption

Propofol is only suitable for intravenous administration and thus does not undergo any absorption interactions. Nonetheless, care should be taken when infusing propofol with other drugs. It is well-described that propofol undergoes chemical interactions with a number of frequently used drugs, and should thus not be administered through the same intravenous line with these particular drugs. Of note are interactions with certain antibiotics (e.g. ciprofloxacin, gentamicin, metronidazole) and calcium antagonists (nimodipine, verapamil). A more extensive list of interactions can be found in the summary of product characteristics (SPC) and in the study by Michaels et al. [155]

7.1.2 Distribution

Propofol is extensively bound to plasma proteins. Concomitant infusion with drugs competing for the same plasma binding sites, or use in patients with low plasma proteins, could potentially result in high unbound plasma propofol fraction, causing more profound effects and adverse effects. The clinical significance of this phenomenon is uncertain [156].

V_d and the rate of metabolism of propofol are affected by drugs affecting the cardiovascular system. Drugs that decrease cardiac output and cause a concomitant decrease in hepatic perfusion alter the distribution and metabolism of propofol, e.g. esmolol [157] and in propofol itself [158, 159]

7.1.3 Metabolism

As with many other drugs used in anaesthesia [160, 161], concomitant administration of propofol with other drugs dependent on metabolism by CYP could interfere with its metabolism. In vitro studies demonstrate this possibility, however the results are not directly transposable to the in vivo situation [162].

7.2 PD Interactions

Propofol interacts with other intravenous and volatile hypnotic drugs, as well as with opioids. In order to mathematically delineate the interaction between different drugs, their combined effectiveness to reach a certain clinically relevant endpoint is assessed. This combined effectiveness can be explored in an isobolographic analysis using isoboles (or 'iso-effective' drug effect dose curves) to show all the

dose combinations of drugs resulting in the same clinical effect [163]. The interaction can also be modelled using a response surface modelling technique [164].

7.2.1 Interactions with Hypnotic Drugs

7.2.1.1 Midazolam A number of studies have investigated the interaction between propofol and midazolam. All studies confirm, as can be expected based on clinical experience, an interaction, however they do not agree on its nature. The study findings range from an additive to synergistic interaction [165–171]. This discrepancy might be due to study methodologies involving inaccurate PK models, or data collection in a non-steady state.

7.2.1.2 Dexmedetomidine Dexmedetomidine is a potent α_2 agonist. Multiple studies have investigated its effect on the propofol concentration necessary to reach specific clinical endpoints. When administered preoperatively, dexmedetomidine reduced the propofol dose necessary for sedation and induction of anaesthesia [172, 173]. In adults, a loading dose of $0.1 \mu\text{g kg}^{-1}$ administered during a 10-min period reduced the half maximal effective concentration (EC₅₀) of propofol for successful i-gel (Intersurgical, Berkshire, UK) airway insertion from 6.75 to $3.18 \mu\text{g/mL}$ [174]; a comparable effect was not found in children [175]. The interaction is also evident during and at the end of anaesthesia. Dexmedetomidine reduced propofol use during spinal surgery under propofol–remifentanyl anaesthesia, and prolonged recovery times at the end of propofol anaesthesia if it was not stopped early [176, 177]. As with midazolam, a clear interaction model has yet to be developed and a well-designed interaction study needs to be performed, preferably using accurate PK models such as the Eleveld model [61] for propofol and the Hannivoort model for dexmedetomidine [35].

7.2.1.3 Volatiles Propofol–sevoflurane interaction studies show an additive interaction, which was demonstrated by studies investigating the effects on clinical endpoints (e.g. loss of consciousness, reaction to laryngoscopy, and reaction to incision), as well as studies measuring the effects on EEG-based parameters from a number of depth of anaesthesia monitors (e.g. Bispectral index, state and response entropy) [178–181]. This additive interaction is not surprising as Sebel et al. demonstrated that propofol and sevoflurane have separate binding sites but converging pathways of action on the GABA α receptor [181, 182].

7.2.2 Interactions with Opioids

Propofol and opioids interact synergistically. This is more pronounced for analgesic drug effects (e.g. loss of response

to noxious stimuli) than for hypnotic clinical endpoints, such as loss of responsiveness to verbal commands [154].

Fentanyl significantly decreases the propofol concentration required for loss of consciousness and suppression of responses to noxious stimuli [183]. A ceiling effect of this interaction is seen at fentanyl effect concentrations of 3 ng mL^{-1} , where the propofol plasma concentration necessary for loss of responsiveness to verbal command is decreased by 40% and the concentration necessary for suppression of movement on incision is decreased by 90% compared with when no fentanyl is administered. Further increases in fentanyl concentrations do not increase interaction effects [184].

Sufentanil showed an additive interaction with propofol with respect to loss of responsiveness to verbal command during the induction of anaesthesia. It reduced the propofol concentration necessary for loss of responsiveness in a dose-dependent manner [185]. Hentgen et al. showed that a sufentanil effect site concentration (C_e) of 0.3 ng/mL combined with propofol C_e of 4 ng/mL provides optimal haemodynamic stability during intubation, while a C_e of sufentanil 0.2 ng/mL provides an optimal balance between haemodynamic stability during operation, and a rapid recovery thereafter [186].

Remifentanyl is an ultra-short-acting opiate. Its interaction with propofol has been extensively studied in regard to multiple clinical endpoints, and it showed a supra-additive interaction with propofol in regard to hypnotic [187] and analgesic [188] endpoints.

8 Methods of Drug Delivery

Administration of intravenous hypnotic drugs brings some unique challenges compared with volatile anaesthetics. Multiphasic PK and the inability to continuously measure the achieved drug concentration can present a challenge when trying to achieve a specific drug effect. In the majority of countries worldwide (the US being the main exception), TCI pumps (infusion pumps programmed to infuse a drug guided by a mathematical PK and PD model so as to achieve a predefined plasma or effect site drug concentration expeditiously) are available in order to simplify the administration of propofol [153, 189]. The most well-known PK/PD models for propofol have already been discussed earlier in this article.

Compliance with ethical standards

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